EXHIBIT 1, Tab 9

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Editorials

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Consequences of Delayed Therapy with Second-line Agents in Rheumatoid Arthritis: A 3 Year Followup on the Hydroxychloroquine in Early Rheumatoid Arthritis (HERA) Study

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ABSTRACT. ***Objective.*** To assess the longterm effect of delaying therapy with second-line agents in patients with early rheumatoid arthritis (RA).

Methods. One hundred nineteen patients who participated in a 9 month placebo controlled randomized trial of hydroxychloroquine sulfate (HCQ) were followed prospectively for an additional 3 years. Those randomized to HCQ are referred to as the early treatment group and those randomized to placebo as the delayed treatment group. Participants were assessed annually for pain [Arthritis Impact Measurement Scales (AIMS) and Stanford Health Assessment Questionnaire (HAQ)], physical disability (AIMS and HAQ), and the RA global well being scale (AIMS). Conversion of results into standard deviation (SD) units permitted defining a substantial difference as per Felson as > 0.30 SD units and a clinically indistinguishable difference as ≤ 0.06 SD units.

Results. One hundred fifteen patients (97%) participated and complete data were available on 104 (87%). Compared to the early treatment group, the delayed group remained worse for both the pain and the physical disability outcomes over the additional 3 year followup. The difference in the RA global well being score became clinically indistinguishable for the early and delayed groups only after the 2 year post-trial assessment. The between-group differences were not explained by post-trial therapy with corticosteroids, other second-line agents, or nonsteroidal antiinflammatory drugs and analgesic preparations.

Conclusion. These findings show that a delay in instituting therapy with second-line agents, even a 9 month delay in instituting a moderately powerful second-line agent such as HCQ, has significant effects on longterm patient outcome, and provides strong evidence in support of early therapy in RA. (J Rheumatol 2000;27:623-9)

Key Indexing Terms:
RHEUMATOID ARTHRITIS HYDROXYCHLOROQUINE RANDOMIZED
HEALTH STATUS TREATMENT DELAY

Over the past decade there has been a radical change in the philosophy of treatment for rheumatoid arthritis (RA). Increasing evidence has accumulated that the traditional approach of watchful waiting prior to the use of second-line agents such as gold salt injections, antimalarial drugs, or immunosuppressive agents results in the inexorable development of physical disability, as well as premature mortality and tremendous financial consequences for patients, their families, and society[1-10].

The traditional restrained approach to the introduction of second-line drugs has been replaced by strong recommendations for early referral of suspected cases of RA and the initiation of second-line therapy within several months of symptom onset. It is thought that there may be a window of opportunity early in the course of RA for the successful introduction of second-line drugs[1-7,11]. Failure to initiate second-line drug therapy early leads to uncontrolled disease activity and the onset of permanent erosions, a feature increasingly recognized to occur early in the disease course of RA and to presage poor outcomes over the long term[1,4,6,12].

Nonetheless, there is only limited evidence that describes the actual effect of delayed treatment. A recent randomized trial of hydroxychloroquine (HCQ) in early RA (the HERA

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study) presented an opportunity to evaluate the effect of a 9 month delay in initiating therapy with a second-line agent on longer term outcome. Given that HCQ, while considered a particularly safe drug, is thought to have only moderate effectiveness as a second-line agent[6,13-17], one might have expected a prompt catch-up in clinical status for those that had been randomized to placebo, but such was not the case. Even 3 years after the completion of the clinical trial, the effect of the 9 month delay in introducing therapy with a second-line agent had not been completely eliminated.

MATERIALS AND METHODS

The HERA study. The design and results of the original randomized, double blind, placebo controlled HERA study have been reported[18]. The HERA study evaluated 119 patients with early RA of < 2 years duration. All patients met established criteria for RA[19]. No participant had previously received a second-line agent. The HERA study revealed statistically significant improvement in 3 composite indices: a joint index composed of the tender joint count, swollen joint count, grip strength, and duration of morning stiffness; a pain index composed of the pain dimension of the Arthritis Impact Measurement Scales (AIMS)[20] and the visual analog pain scale of the Health Assessment Questionnaire (HAQ)[21]; and a physical function index composed of the HAQ, the physical dimension of the AIMS and the McMaster-Toronto Arthritis Patient Performance Disability Questionnaire (MACTAR)[22].

The extended study. All 119 participants who completed the initial HERA trial were invited prospectively to participate in an extended followup program. At 3 annual intervals after completion of the trial (1.75, 2.75, and 3.75 yrs after randomization) consenting participants were assessed for pain (AIMS and HAQ), physical disability (AIMS and HAQ), and the 100 mm visual analog RA global well being scale from the AIMS.

No attempt was made to constrain the treatment that study participants received after the completion of the 9 month double blind portion of the HERA study. At the annual post-trial followup, data were obtained on all medications used for the arthritis as well as other conditions.

The study was approved by the Research Ethics Committee of the Montreal General Hospital Research Institute.

Sample size and analysis. A standardization technique identical to that used in the original HERA report was used[18]. The standardization permitted combination of results from different scales into a single index, allowed for easier comparison across different outcomes, and facilitated the interpretation of the effect of delay in institution of therapy upon outcome. Thus, standardization permitted combination of the results of the 2 measures of physical disability (HAQ and AIMS) into a physical function index and the 2 pain measures (HAQ and AIMS) into a pain index. Comparison across outcomes is improved as all outcomes are expressed in identical units [standard deviation (SD) units].

While a number of different criteria exist for determining what is a clinically significant difference in RA[23-25], no criteria exist for clinical identity. Yet to determine when differences disappear, it is necessary to determine when differences become clinically indistinguishable or immaterial. Felson, *et al*[13] have noted that for RA a difference of 0.30 SD units is substantial (e.g., in Felson's metaanalysis, the effect of auranofin on a global outcome was 0.21 and of methotrexate (MTX) was 0.48 SD units compared to placebo). We arbitrarily determined that a difference would be clinically immaterial if it were one-fifth of a substantial difference, that is, one-fifth of 0.30 SD units or 0.06 SD units. Using the method described by Spiegelhalter, *et al*[26], we defined a range of clinical equivalence for between-group differences to be between 0.06 and -0.06 SD units. We then calculated the probabilities that true differences were > 0.06 SD units in favor of HCQ at every followup for each of the 4 standardized outcomes. Each probability is calculated as the proportion of the probability density curve for that parameter that falls below the 0.06 cutoff. Therefore, the set of calculated probabilities are directly interpreted as the probability that the 2 groups have become "equivalent" for each outcome measure at each point in time. For comparison, we repeated this analysis for between-group differences of ≥ 0.30 SD units, a difference considered substantial.

Standardized scores were calculated as follows: For each patient the actual value for a component variable at each visit was subtracted from the baseline value at each visit. The resultant number was then divided by the SD at baseline for all patients. Thus, the transformed values for each patient for a given variable measured their changes from baseline in SD units. In particular, all scores are necessarily zero at baseline. For all variables analyzed, raw scores increase as a patient's condition worsens, and negative standardized scores indicate improvement from baseline values. For the physical disability and pain outcomes that were based on index scores, the index score was calculated as the average of the standardized scores of the component variables.

To assess whether the results obtained in this study could be explained by therapy received by the 2 randomized treatment groups post-trial, use of corticosteroids (oral or injected) and second-line agents (HCQ, gold, MTX, sulfasalazine, azathioprine, D-penicillamine) was compared. This analysis was performed a number of different ways. We compared the number of patients that received corticosteroids or second-line agents (alone or in combination) at each followup, as well the total number of patients that ever received any of the treatments by chi-square test. Also, between-group differences in duration of therapy with oral corticosteroids or each or any second-line agent were analyzed. Finally, cumulative doses of oral corticosteroids and each of the second-line agents, total number of second-line agents used by each patient, and total number of corticosteroid injections received were also compared. Student's t test was used for between-group comparisons of continuous variables.

An intent-to-treat approach in which all patients are maintained in the original groups to which they had been randomized was used for all the analyses. The sample size for the present study was fixed by the original HERA study. As a result, the outcomes for the extended study are presented largely for descriptive purposes, in that the study population was not assembled with the longterm outcomes evaluated in the present report in mind.

RESULTS

Randomization succeeded in assembling 2 groups of patients with similar characteristics (Table 1). Three-quarters of the participants were women. At randomization, the average age was 53 years and the mean joint count was 26, out of a maximum possible of 60. The average duration of RA from the first onset of polyarthritis was 9.2 months. For the purposes of this extension of the trial, those randomized to receive HCQ are referred to as the early treatment group and those randomized initially to placebo are called the delayed treatment group.

Four (3%) of the original 119 patients did not participate in the extension phase of the study. Three declined to participate (one early and 2 delayed) and one patient in the delayed group died of chronic obstructive pulmonary disease during the initial trial. An additional 11 (9%) contributed only partial data to the study because they did not complete the extended followup. Among these 11 patients, 2 from the delayed treatment group and 3 from the early therapy group died before the end of the study, and 3 patients in each group dropped out before completing the followup study. Thus, partial data were available on 115

Table 1. Characteristics of patients at randomization, by treatment group. Plus–minus values are means ± one standard deviation.

Characteristic	Early, n = 58	Delayed, n = 57
Age, yrs	53 ± 14	52 ± 15
Female sex, no. (%)	44 (76)	43 (75)
Education, yrs	11.3 ± 2.7	10.5 ± 3.2
Duration of RA, mo	8.9 ± 5.8	9.4 ± 5.9
Tender joint count, 0–60	25.3 ± 13.5	25.7 ± 14.2
RF positive, no. (%)	24 (41)	31 (54)
ESR, mm/h	32.6 ± 14.6	32.8 ± 16.9
Arthritis Impact Measurement Scales		
Physical disability, 0–10	2.47 ± 1.47	2.52 ± 1.56
Psychological disability, 0–10	3.22 ± 1.62	3.37 ± 1.87
Pain, 0–10	6.49 ± 1.65	6.42 ± 1.76
Global well being, 0–100	41.6 ± 22.0	42.1 ± 21.9
Health Assessment Questionnaire		
Physical disability, 0–3	1.05 ± 0.60	0.97 ± 0.58
Pain, 0–3	1.46 ± 0.71	1.36 ± 0.72

RF: rheumatoid factor, ESR: erythrocyte sedimentation rate.

(97%) and complete data on 104 (87%) of the original 119 patients.

The standardized scores for the pain index, the physical function index, and the RA global well being scale appear to show greater improvement for the early compared to the delayed treatment group for much if not all of the 3 years of extended followup (Table 2). The probability estimates for a clinically immaterial difference (0.06 SD units), the outcome statistic to determine when the delayed therapy group "caught up" with the early treatment group, are shown for the pain index (Figure 1), the physical function index (Figure 2), and RA global well being (Figure 3).

In addition, the probability estimates for a substantial clinical difference (0.30 SD units) are depicted in these same figures. For the pain index (Figure 1) and the physical function index (Figure 2), the probability is at least 50% that the difference between the early and the delayed treatment groups was more than clinically immaterial throughout the followup (the probabilities at 9, 21, 33, and 45 months are all > 0.50 that the clinical difference exceeded 0.06 SD units in favor of the early treatment group). For RA global well being (Figure 3), it is only some time after 33 months that patients initially randomized to placebo "caught up" with the early treatment group randomized initially to HCQ (the probability is < 50% of the difference being greater than clinically immaterial).

Indeed, for the pain index and RA global well being score, not only was the difference > 0.06 SD units, but for much of the followup period the difference in favor of the early treatment group was clinically substantial (the probability exceeded 50% that the difference is > 0.30 SD units). Thus, a clinically substantial difference in the pain index persisted for at least 33 months and for the RA global well being scale persisted for at least 21 months.

Because differences in treatment with second-line agents or corticosteroids for the 3 years after the randomized study might have explained the retardation in the delayed treatment group catching up with the early treatment group, this was analyzed extensively. We looked for differences in the frequency of use, duration of use, or cumulative dose of second-line agents, either alone or in combination, or of oral or injected corticosteroids, for the 3 years after the 9 month placebo controlled portion of the study. HCQ was used for a longer duration in the early treatment group than the delayed therapy group (22 ± 19 vs 15 ± 16 months, respectively; p = 0.03, Student's t test) (Table 3). This was not unexpected, as the early treatment group had been randomized to HCQ and were thus more likely to continue taking this agent. There were no differences in the use of corticosteroids, MTX, intramuscular gold, or other second-line agents.

DISCUSSION

These results suggest that, in the 3 year period after the conclusion of the 9 month placebo controlled portion of the HERA study, patients randomized to the placebo group, and hence in whom treatment with second-line agents had been delayed, did not catch up with the early treatment group

Table 2. Pain, physical disability, psychological disability, and global well being in standard deviation units, by randomized treatment group. Plus–minus values are means ± one standard deviation.

Variable	Treatment Group	Month 9	21	33	45
Pain index	HCQ	−1.23 ± 1.04	-1.36 ± 1.02	−1.32 ± 1.34	−1.29 ± 1.34
	Placebo	-0.058 ± 1.17	−0.076 ± 1.12	−0.90 ± 1.23	−1.09 ± 1.31
Physical disability index	HCQ	−0.57 ± 0.94	−0.58 ± 0.95	−0.60 ± 1.08	−0.48 ± 1.21
	Placebo	−0.31 ± 1.09	−0.33 ± 1.01	−0.36 ± 1.08	−0.40 ± 1.14
Psychologic disability	HCQ	−0.44 ± 0.95	−0.52 ± 0.94	−0.61 ± 1.23	−0.36 ± 1.10
	Placebo	−0.41 ± 1.04	−0.55 ± 0.86	−0.48 ± 0.94	−0.55 ± 1.16
RA effect on global well being	HCQ	−0.50 ± 0.86	−0.65 ± 0.98	−0.69 ± 1.20	−0.59 ± 1.17
	Placebo	0.02 ± 1.12	−0.28 ± 1.10	−0.44 ± 1.08	−0.58 ± 1.11

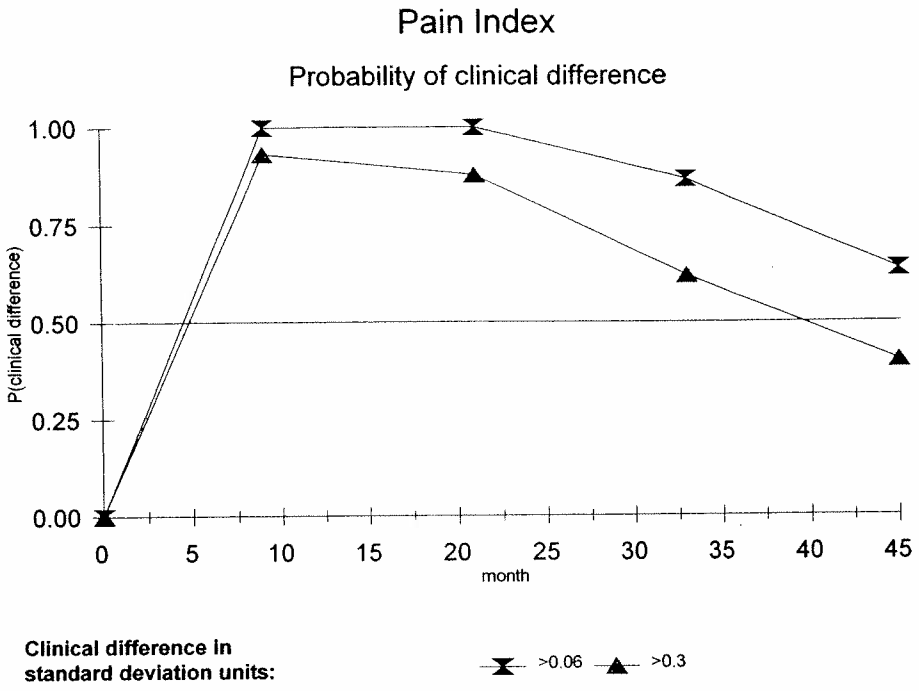

Figure 1. The probability (y axis) of a clinical difference > 0.06 SD units (⧗) or > 0.30 SD units (▲) for the pain index over the course of the study (x axis). When the symbol is above the line at P(clinical difference) = 0.50, one is at least 50% certain that the difference between early and delayed treatment groups was more than clinically immaterial.

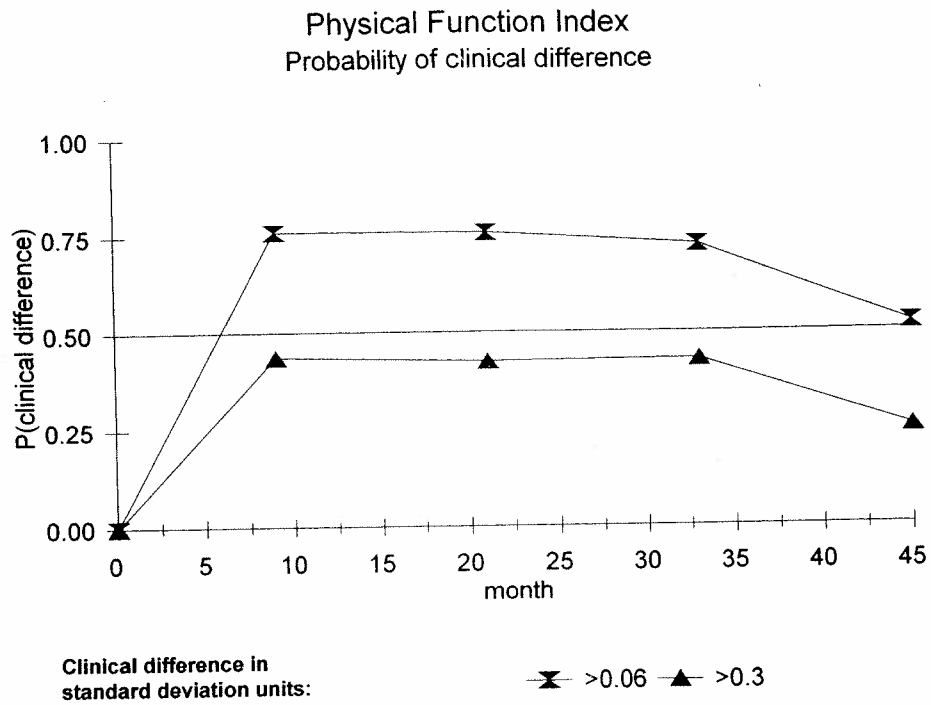

Figure 2. The probability (y axis) of a clinical difference > 0.06 SD units (⧗) or > 0.30 SD units (▲) for the physical function index over the course of the study (x axis). When the symbol is above the line at P(clinical difference) = 0.50, one is at least 50% certain that the difference between early and delayed treatment groups was more than clinically immaterial.

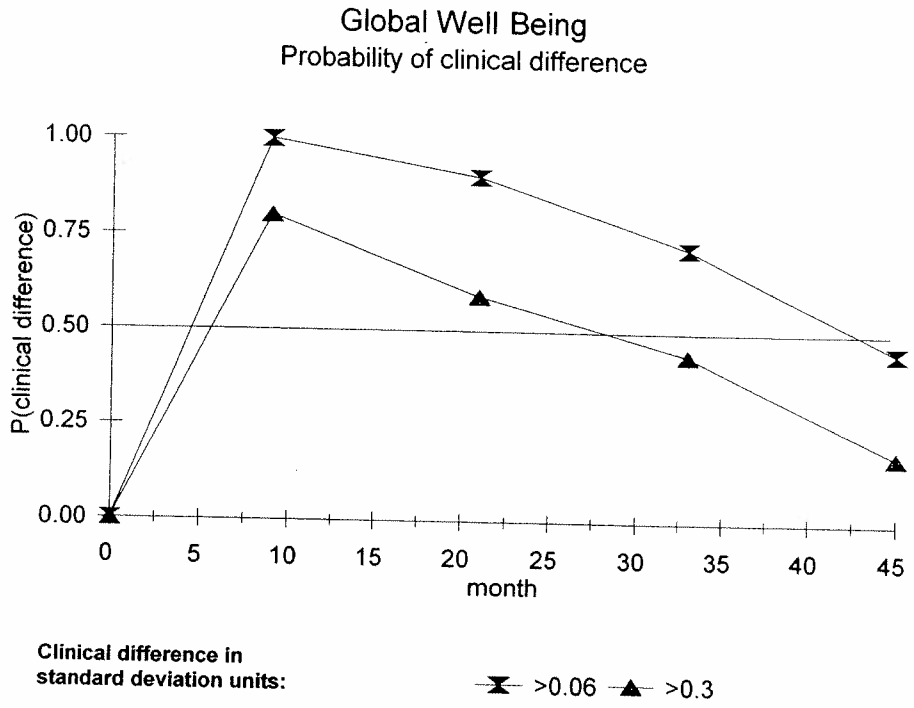

Figure 3. The probability (y axis) of a clinical difference > 0.06 SD units (⧗) or > 0.30 SD units (▲) for global well being over the course of the study (x axis). When the symbol is above the line at P(clinical difference) = 0.50, one is at least 50% certain that the difference between early and delayed treatment groups was more than clinically immaterial.

Table 3. Post-randomized trial treatment for RA, by initial randomized group.

Treatment	Patients Treated, months		Mean (± SD) Duration of Treatment, months	
	HCQ	Placebo	HCQ	Placebo
Second-line agents				
HCQ	39	32	22 ± 19	15 ± 16*
Methotrexate	14	17	5 ± 12	7 ± 12
IM gold	9	10	4 ± 11	5 ± 13
Other**	8	12	2 ± 6	4 ± 10
Any second-line agent	52	46	31 ± 18	27 ± 19
Corticosteroids				
Oral	8	11	4 ± 11	4 ± 11
Injected	20	28	—	—

*p = 0.03, Student's t test. **Includes oral gold, sulfasalazine, azathioprine, D-penicillamine.

randomized to HCQ. For the pain index and the physical disability index they did not catch up during the followup period and for the RA global well being scale they did not catch up for at least 2 years after the randomized trial ended.

For the 3 years after the randomized trial, the 2 groups were treated similarly with oral and injected corticosteroids and with second-line drugs. That the early treatment group received HCQ for a longer duration during the 3 year followup is not surprising, as patients in this group had been randomized to early treatment with HCQ and were more likely to continue taking it. Over all, treatment differences following the randomized trial are not a likely explanation for the sustained clinical differences observed.

Recently, a consensus has developed that to prevent longterm disability, to reduce premature mortality, and to reduce costs in RA, treatment with second-line agents should be introduced early in the course of RA — within months of the first onset of the disease — and maintained as

long as there is evidence of disease activity. Two retrospective studies address the question of maintaining treatment with second-line agents. Ward, *et al*[27] found that patients with RA treated regularly by a rheumatologist had a significantly lower rate of development of disability than patients evaluated intermittently. This difference was associated with more intensive use of second-line agents and use of joint surgery in those receiving regular rheumatologic care. Fries, *et al*[28] showed that consistent use of second-line agents could reduce longterm disability by up to 30%. These studies provide evidence that over an average period of up to 10 years, appropriate management with second-line drugs reduces disability. The prolonged disease activity seen in the present study suggests that additional morbidity will be the longterm result even though the delayed therapy group may eventually "catch up" with the early treatment group for all outcomes.

Participants in the studies by Ward, *et al*[27] and Fries, *et al*[28] had had their RA an average of 10 years and thus some caution should be exercised in extrapolating the results to the issue of early intervention. Indeed, it is only recently that there has been any evidence that treatment of early disease was effective. Most studies in early RA (generally defined as within one or 2 yrs of disease onset), including the initial HERA report[18], have been short term studies of a year or less duration[29-35]. Thus, double blind placebo controlled treatment studies in early RA with HCQ[18], auranofin[29], sulfasalazine[30,31], minocycline[32], and prednisolone[33] have shown that these agents are effective for at least some outcomes. Similarly, a step-down protocol of combination MTX, prednisolone, and sulfasalazine was superior to sulfasalazine alone[34]. An open randomized study that compared one of a number of second-line drugs, including HCQ, intramuscular gold, or MTX, showed that this strategy was superior to no treatment with a second-line drug[35]. These studies show that second-line agents are effective in early RA, but do not address the longterm consequences of failing to institute second-line therapy early.

The only study that has examined the longer term consequence of delaying treatment with a second-line agent is that of Egsmose, *et al*[11]. These investigators obtained prospective data for 5 years after randomization on 75 of the original 137 (55%) patients evaluated in a clinical trial of auranofin in early RA[29]. Using area under the curve analytic techniques, they reported that an average 8 month delay in the initiation of therapy with auranofin resulted in statistically significant differences for swollen joint count, Ritchie joint index, Keitel functional index, and Beck depression scale that favored the early over the delayed treatment group. Morning stiffness, grip strength, pain, and the HAQ physical disability index score did not differ significantly. Also, Egsmose, *et al* showed statistically significant worse progress in radiographic erosions in the delayed therapy group. When an identical analysis was conducted with our data, we found similar results. Patients randomized to receive early treatment had significantly less pain and a trend to a greater sense of global well being than those randomized to placebo over the 3.75 year followup period. The physical disability index favored early treatment, but the results were not significant (data not shown).

We conclude that even a 9 month delay in instituting therapy with a moderately effective second-line agent such as hydroxychloroquine can lead to disease activity that may be more difficult to bring under control than would have been the case had treatment been started earlier. This results in pain, physical disability, and a lack of well being that is more prolonged than might have been expected. The findings provide additional support for the prompt diagnosis and early institution of second-line treatment in RA.

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APPENDIX

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REFERENCES

1. Harris ED Jr. Rheumatoid arthritis: pathophysiology and implications for therapy. N Engl J Med 1990;322:1277-89.
2. Wolfe F, Hawley DJ, Cathey MA. Clinical and health status measures over time: prognosis and outcome assessment in rheumatoid arthritis. J Rheumatol 1991;18:1290-7.
3. Guillemin F, Suurmeijer T, Krol B, et al. Functional disability in early rheumatoid arthritis: description and risk factors. J Rheumatol 1994;21:1051-5.
4. Emery P, Salmon M. Early rheumatoid arthritis: time to aim for remission? Ann Rheum Dis 1995;54:944-7.
5. Emery P, Symmons DPM. What is early rheumatoid arthritis?: definition and diagnosis. Baillieres Clin Rheumatol 1997;11:13-26.
6. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for the management of rheumatoid arthritis. Arthritis Rheum 1996;39:713-22.
7. Stucki G. Specialist management: needs and benefits. Baillieres Clin Rheumatol 1997;11:97-107.
8. Clarke A, Zowall H, Levinton C, et al. Direct and indirect medical costs incurred by Canadian patients with rheumatoid arthritis. J Rheumatol 1997; 24:1051-60.
9. Gabriel SE, Crowson CS, Campion ME, O'Fallon WM. Direct medical costs unique to people with arthritis. J Rheumatol 1997;24:719-25.
10. Gabriel SE, Crowson CS, Campion ME, O'Fallon WM. Indirect

and nonmedical costs among people with rheumatoid arthritis and osteoarthritis compared with nonarthritic controls. J Rheumatol 1997;24:43-8.
11. Egsmose C, Lund B, Borg G, et al. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup of a prospective double blind placebo controlled study. J Rheumatol 1995;22:2208-13.
12. van der Heide A, Remme CA, Hofman DM, Jacobs JWG, Bijlsma JWJ. Prediction of progression of radiologic damage in newly diagnosed rheumatoid arthritis. Arthritis Rheum 1995;38:1466-74.
13. Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis: results of two metaanalyses. Arthritis Rheum 1990;33;1449-61.
14. Harris ED Jr. Hydroxychloroquine is safe and probably useful in rheumatoid arthritis [editorial]. Ann Intern Med 1993;119:1146-7.
15. Anonymous. Drugs for rheumatoid arthritis. Medical Lett 1994; 36:101-6.
16. Scott DL. Clinical guidelines for management. Baillieres Clin Rheumatol 1997;11:157-79.
17. Clark P, Casas E, Tugwell P, et al. Hydroxychloroquine compared with placebo in rheumatoid arthritis: a randomized controlled trial. Ann Intern Med 1993;119:1067-71.
18. The HERA Study Group. A randomized trial of hydroxychloroquine in early rheumatoid arthritis. Am J Med 1995;98:156-68.
19. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
20. Meenan RF, Gertman PM, Mason JH. Measuring health status in arthritis: the Arthritis Impact Measurement Scales. Arthritis Rheum 1980;23:146-52.
21. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the Health Assessment Questionnaire, disability and pain scales. J Rheumatol 1982;9:789-93.
22. Tugwell P, Bombardier C, Buchanan WW, Goldsmith CH, Grace E, Hanna B. The MACTAR Patient Preference Disability Questionnaire — an individual approach to assessing improvement in physical disability in clinical trials in rheumatoid arthritis. J Rheumatol 1987;14:446-51.
23. Paulus HE, Egger MJ, Ward JR, Williams HJ, and the Cooperative Systematic Studies of Rheumatic Diseases Group. Analysis of improvement in individual rheumatoid arthritis patients treated with disease-modifying anti-rheumatic drugs, based on the findings in patients treated with placebo. Arthritis Rheum 1990;33:477-504.
24. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
25. van Gestel AM, Prevoo MLL, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism criteria. Arthritis Rheum 1996;39:34-40.
26. Spiegelhalter DJ, Freedman LS, Parmar MKB. Bayesian approaches to randomized trials. J Roy Stat Soc A 1994; 157:357-416.
27. Ward MM, Leigh JP, Fries JF. Progression of functional disability in patients with rheumatoid arthritis: associations with rheumatology subspecialty care. Arch Intern Med 1993; 153:2229-37.
28. Fries JF, Williams CA, Morfeld D, Singh G, Sibley J. Reduction in long-term disability in patients with rheumatoid arthritis by disease-modifying antirheumatic drug-based treatment strategies. Arthritis Rheum 1996;39:616-22.
29. Borg G, Allander E, Lund B, et al. Auranofin improves outcome in early rheumatoid arthritis. Results from a 2-year, double blind, placebo controlled study. J Rheumatol 1988;15:1747-54.
30. The Australian Multicentre Clinical Trial Group. Sulfasalazine in early rheumatoid arthritis. J Rheumatol 1992;19:1672-7.
31. Hannonen P, Möttönen T, Hakola M, Oka M. Sulfasalzine in early rheumatoid arthritis: a 48-week double-blind, prospective, placebo-controlled study. Arthritis Rheum 1993;36:1501-9.
32. O'Dell JR, Haire CE, Palmer W, et al. Treatment of early rheumatoid arthritis with minocycline or placebo: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 1997;40:842-8.
33. Kirwan JR and the Arthritis and Rheumatism Council Low-dose Glucocorticoid Study Group. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. N Engl J Med 1995;333:142-6.
34. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalzine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309-18.
35. van der Heide A, Jacobs JWG, Bijlsma JWJ, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med 1996;124:699-707.